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# THE VACCINE TREATMENT OF GONOCOCCAL INFECTIONS WITH SPECIAL REFERENCE TO DETOXICATED VACCINES

Based upon an Address delivered before the Medical Society for the Study of Venereal Diseases on February 27th, 1925, by DAVID THOMSON, O.B.E., M.B., Ch.B., D.P.H.

IF we examine the voluminous literature dealing with the treatment of gonococcal infections by specific vaccines, it is found that over 90 per cent. of the authors maintain that vaccine therapy is of value in this disease.

Certain authorities believe that the most satisfactory vaccines are those which consist of the whole dead germs unchanged and untreated in any manner ; some believe in sensitised vaccines, and more recently there has been a tendency to believe in "non-specific vaccines," and "non-specific proteins." Thus good results have been claimed in the treatment of gonorrhœa by means of injections of typhoid vaccine, and others have obtained beneficial results from injections of milk.

For some years past the author has concluded from his own researches that the raw natural vaccines, so to speak, composed of the whole dead germs, are not necessarily the best. Extensive researches carried out at the Military Hospital, Rochester Row, during the war showed that gonococcal vaccine from which the toxin had been removed, by a special process, still remained antigenic as proved by the complement-fixation test, carried out in a large series of cases.

Parallel experiments by Dr. Lees showed that a series of patients who were treated by detoxicated gonococcal vaccine got better more rapidly than a series which received the ordinary toxic vaccine, and that the duration of the illness in these two series was shorter than in a series of cases which were not treated by any kind of vaccine at all.

The clinical and laboratory findings in these series of cases were in agreement and confirmed each other.

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Much work has been done with other vaccines in attempts to improve the antigenic results obtained by their administration. Many products derived from the tubercle bacillus have been claimed to have a curative influence upon tuberculosis, and to-day there are many varieties of tuberculin upon the market.

Over a year ago Professor Dreyer claimed that "defatted vaccines," wherein the bacteria had been deprived of their resistant lipoidal or waxy covering, were much superior to vaccines composed of the natural unchanged germs.

If all vaccines composed of the given natural unaltered bacteria were satisfactory, these problems of improving them would not have arisen, but the fact remains that the majority of the natural vaccines are not nearly so satisfactory as we would like them to be. A most important problem, therefore, lies before us.

Germs can be split up by various processes into their component substances. Are all of these components antigenic, or are some of them useless as immunising agents? Is it impossible to split away or extract from the germs some powerful immunising and non-poisonous fraction which can be injected into the human being in large doses without harmful results, or is the whole unaltered germ always a more satisfactory vaccine than any given fraction thereof? Considerable evidence has been brought forward by many workers that certain fractions of bacteria are good antigens, whilst other fractions have little or no immunising value. There are, however, many ways of splitting germs into their component fractions, but some of these cleavage processes would be useless for the end we have in view, since they destroy much of the antigenic properties of the original material. It is very important, therefore, to find a method of separating, in more or less pure form, the various antigenic portions of the bacteria without thereby damaging or weakening the immunising properties of such fractions.

In attempting to elucidate these problems, it is necessary to carry out numerous original experiments which would appear to bear on the subject. It is also necessary to search diligently in the vast store-house of existing records of experiments carried out during the past forty years on immunity. A thorough grasp of all information of this nature is necessary in order to indicate the lines of future research on this subject.

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The writer has collected much information on the biochemistry of bacteria with special reference to their antigenic properties. It is impossible, however, to consider here all the data available. A review of the mass of work as a whole, however, leaves no doubt whatever that certain fractions of germs are antigenic and immunising, whether they are split off by a certain process or extracted by some solvent agent.

A large amount of controversy and divergence of opinion has arisen over these questions, and this will continue so long as our knowledge upon the subject is so incomplete. Dreyer, for example, has suggested that the lipoidal substance is useless in immunity; others disagree. I myself, with others, have suggested that the toxic material of the germ is not only useless but harmful; others, on the contrary, would appear to believe that the toxic fraction is all-important in the production of immunity, and each side can bring forward arguments in favour and against. There is no doubt that much can be done in the laboratory by experiments on animals to elucidate these problems, and it is largely from such laboratory tests that the bacteriologist draws his conclusions. Unfortunately, animals are not susceptible to gonorrhœa, so experiments of this nature are more or less out of the question. Immunity estimations in the case of the gonococcus have, therefore, to be carried out on the human subject. Another difficulty arises from the fact that many experienced clinicians maintain that the conclusions deduced from the test-tube and from laboratory animals do not necessarily hold good when they come to be applied to the human subject. We know, for example, that a given dosage of a therapeutic agent as estimated by animal experiment does not necessarily work out correctly weight for weight when applied to the human subject. Further, though an antiseptic may kill a bacterium in the test-tube, we cannot argue from this that it will kill this same organism in the human subject.

Although, therefore, suggestions and deductions may arise in the laboratory as a result of *in vitro* and animal experiments, the final proof must always come from the physician himself. I have not carried out any very extensive investigations on the antigenic properties of detoxicated gonococcal vaccine since I was at the Military Hospital, Rochester Row, chiefly owing to the fact that I

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have not had access to in-patients, and it is useless to carry out careful laboratory tests, after vaccine injections, on out-patients. My brother, Dr. Robert Thomson, has done a certain amount of work on this matter which has more or less confirmed my previous work. My own personal efforts have been directed more towards improving the process of detoxication, by using weaker and still weaker chemicals in this process, in order to remove the toxins more and more by mechanical means and less by the agency of chemicals.

Although many physicians have informed me that they are satisfied that detoxicated vaccines of many varieties give excellent therapeutic results, several of them believe that the detoxicated gonococcal vaccine is superior in its class to detoxicated vaccines prepared from other organisms. It is quite probable that this is correct. The gonococcus is very soluble in alkali, and can be dissolved and detoxicated with the use of alkali as weak as N/50 NaOH, which is about 0.1 per cent. strength.

Other germs, on the contrary, such as pneumococci, streptococci, tubercle bacilli, etc., require much stronger alkali than 0.1 per cent. to disintegrate them, even with the aid of mechanical action. It is quite probable, therefore, that detoxicated vaccines prepared from such bacteria, where fairly strong alkali is used, will not be so efficient as the detoxicated gonococcal vaccine.

Two papers have recently appeared (*Brit. Med. Jour.*, December 13th, 1924), one by Dr. Davidson and the other by Dr. Campbell, in which it is inferred from laboratory tests that the detoxication process largely damages the antigenic properties of the organisms. The germs which were used were *B. suipestifer* (Dr. Davidson) and *B. typhosus* (Dr. Campbell). The latter found that detoxicated *B. typhosus* vaccine did give rise to the formation of agglutinins. I agree that the detoxication process diminishes very considerably the agglutinin-producing power of typhoid vaccine, though my own experiments showed that they were by no means destroyed altogether.

It is, however, well known that immunity to typhoid fever does not depend upon the amount of agglutinin present in the blood. Indeed, some assert that the agglutinin has no connection with the immune body. I do not, however, feel competent to speak on this matter,

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nor have I had any personal experience on the efficiency of detoxicated typhoid vaccine. I have had, however, considerable experience with many other detoxicated vaccines which require in the process of detoxication the use of alkali quite as strong as is used in the case of the typhoid bacillus and *B. suipestifer*, and these vaccines certainly produce good therapeutic and immunising results. As examples, I will mention detoxicated anti-catarrhal vaccines and detoxicated tubercle bacillus vaccine. With regard to the latter vaccine, successful results have been obtained in the immunisation of calves against tuberculosis, and young cows which gave positive tuberculin and Calmette tests were rendered negative to these tests after treatment with the vaccine. If, therefore, it would appear that detoxicated vaccines of germs requiring the use of strong alkali give good immunising results, then one would expect detoxicated gonococcal vaccine, where extremely weak alkali is used, to be very highly antigenic.

There has been a considerable divergence of opinion in the past as to the correct dosage of vaccines. Some recommend extremely minute doses of, say, half a million germs, whereas others say that doses up to 500 millions to 1,000 millions should be given. For immunisation purposes I agree with large doses, and that is the aim of detoxicated vaccines, viz., removal of the poison, so that very large doses equal to even 50,000 million organisms may be given.

The writer (*vide* "Gonorrhœa," Thomson, 1923; also *Annals of the Pickett-Thomson Research Laboratory*, 1924, vol. i., No. 1) has carried out a considerable number of experiments on the amount of hæmolysin produced when sheep red cells are injected into rabbits. It was found that minute doses of sheep corpuscles equal in amount to the dosage of toxic vaccines produced no detectable hæmolysin, whereas doses equal to the doses of detoxicated vaccines produced a considerable amount of hæmolysin, and larger doses produced still more. This is sufficient to show that dosage is an extremely important matter. Further experiments were carried out which showed that strong alkali deteriorated the antigenic properties of the sheep cells, whereas weak alkali, N/20 NaOH or less, had little or no deleterious action in this respect. The aim, therefore, has been to give enor-

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mous doses of detoxicated gonococcal vaccine, and to use extremely weak alkali in the detoxication process. Although I have always been an advocate of large doses, I am nevertheless well aware that extremely small doses may often have a beneficial therapeutic effect, which would appear to be explained by the phenomenon termed "desensitisation." It is now well known that tiny doses of vaccine tend to render the individual insensitive towards the bacteria injected. This denotes that some change has been produced in the system which may be of therapeutic value.

### OTHER PROBLEMS IN VACCINE THERAPY

The vaccine treatment of a given disease would be a simple matter if the disease were due to a single germ, and if we possessed a very efficient vaccine prepared from that germ. Unfortunately, however, in the majority of infective diseases we have to deal with an attack on the tissues by many varieties of bacteria at the same time, so that vaccine treatment requires the inoculation of efficient multiple antigens.

A single germ, such as the gonococcus, the tubercle bacillus, etc., is often the attacking agent which initiates the commencement of the illness. Very soon after the disease has started it becomes, however, a mixed infection, because several varieties of secondary organisms, such as staphylococci, streptococci, diphtheroids, etc., now gain a foothold on the tissues, devitalised by the primary attacking organism. Therapeutic treatment by a vaccine of the attacking germ alone is, therefore, no longer sufficient, especially in chronic cases, and it becomes necessary to use a compound vaccine of all of the organisms present.

### CONCLUSIONS

(1) There can be no doubt that good results are obtained by vaccine therapy in the treatment of gonococcal infections.

(2) Much research is still required in this direction ; thus we must try to develop satisfactory methods of preparing highly efficient antigenic vaccines. This knowledge can be much enhanced by a serious study of the biochemistry of the bacteria themselves.

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(3) Lastly, further research is required with regard to the secondary organisms which follow in the wake of the gonococcus, and which often remain long after the gonococcal infection has been eradicated.

Very little work has in reality been done upon these secondary infections.